REMARKS

Reconsideration of this application is respectfully requested. Claims 1-10, 20-25, 27-29, 31-37, 40-44, 51 and 52 are pending and at issue.

The presently claimed invention is a tablet comprising tacrolimus dispersed in a vehicle of polyethylene glycol (PEG) having an average molecular weight of at least 1500 and a poloxamer. The tablet releases less than 20% w/w of the tacrolimus within 30 minutes (when subjected to an *in vitro* dissolution test using USP Paddle method and using 0.1 N HCl as dissolution medium). The present inventors have surprisingly discovered that tacrolimus dispersed in a mixture of PEG and poloxamer results in enhanced bioavailability of the poorly soluble drug tacrolimus, and is well suited for use in controlled release tacrolimus tablets.

Obviousness Rejection Over Yamashita in view of Koretke

Claims 1-10, 20-25, 27-29, 31-37, 40-44, 51 and 52 stand rejected under 35 U.S.C § 103(a) as obvious over Yamashita (EP 1064942) in view of Koretke (WO 01/95939). According to the Examiner, Yamashita discloses a tacrolimus tablet with particulate components and PEG with a molecular weight above 1500.[1] *See* page 4 of the June 7, 2010 Office Action. The Examiner acknowledges that Yamashita does not disclose a mixture of PEG and poloxamer. The Examiner contends that Koretke discloses controlled release formulations containing an active agent, PEG and a poloxamer and thus concludes that it would have been obvious to incorporate the Koretke hydrophilic components in the Yamashita tacrolimus formulation. Applicants respectfully disagree.

First, Yamashita does not disclose poloxamer. Furthermore, as acknowledged by the Examiner, Yamashita does not disclose a mixture of poloxamer and PEG as recited in the pending claims.

[1] The June 7, 2010 Office Action states that Yamashita discloses a controlled release tacrolimus formulation comprising various hydrophilic and hydrophobic components, and that the "hydrophilic components include [PEG] with a molecular weight of 4000 along with Gelucire polymers" (page 4, first full paragraph). Applicants' representative, however, has been unable to locate any disclosure in Yamashita of Gelucire polymers.

Second, a skilled artisan would not have combined the formulation of Koretke with that of Yamashita. Yamashita is directed to a *sustained release* formulation of a macrolide compound (abstract and paragraph [0003] (page 1)), while Koretke is directed to a *fast release* formulation (abstract; page 1, lines 4-5; page 2, lines 27-30).

> "[The invention of Koretke] enables the solid dispersion to be a fast-release solid dispersion formulation, whereas typical solid dispersions enhance solubility, and therefore bioavailability, but are slow release formulations.

(Koretke, p. 3, lines 22-24). A skilled artisan would, therefore, not have had any motivation to incorporate a fast release formulation as taught in Koretke into the sustained release formulation of Yamashita. Further, unlike Koretke, the presently claimed tablet provides slow release of tacrolimus. Specifically, the presently claimed tablet releases less than 20% of the tacrolimus after 30 minutes under specified *in vitro* dissolution conditions.

Additionally, the formulation in Koretke cannot readily be formed into a tablet due to its high PEG content (≥ 60%). *See* Dr. Reza Fassihi's declaration attached to Applicants' January 8, 2010 response. The Examiner states that Dr. Fassihi's conclusion assumes that compression or compaction tabletting techniques are used. Notably, the most commonly used method for making tablets is with a punch-and-die (i.e., compression tabletting). *See* Remington: The Science and Practice of Pharmacy, 21st Ed. (2006), p. 889 ("The vast majority of tablets commercialized today are compressed tablets, either in an uncoated or coated state").

Koretke also expressly distinguishes his capsules (and molds) from tablets:

> Preferred solid dispersions of this invention may be filled into capsules or molds prior to solidfication. Alteration of the solid dispersion by physical means (i. e., additional energy added) from the original cooled solid form yielded drastically different solubilization due to uncontrolled erosion rate and nucleation of the drug substance in the milled high surface area formulation. **This property distinguishes this invention from known solid dispersion dosage forms in which solid dispersion of drug and PEG were milled and filled into capsules or tableted.**

(Koretke, p. 6, lines 31-38) (emphasis added). As stated by Koretke, alteration of the solid dispersion by physical means (such as by compression as recited in claim 37) can yield "drastically different solubilization" of the drug due to an uncontrolled erosion rate and nucleation (i.e., crystallization) of the drug.

Koretke is also completely silent regarding a tacrolimus composition of any kind, let alone a tacrolimus tablet, as presently claimed. Koretke merely discloses that his invention is useful for "any poorly soluble, poorly wettable compound that melts without decomposition below the flash point of polyethylene glycol." *See* Koretke at page 4, lines 22-24. Applicants submit that this blanket statement regarding compounds that may be used in the Koretke invention would not in any way lead one of ordinary skill in the art to select tacrolimus, as required by the present claims. Indeed, the only drug exemplified by Koretke is (S)-(-)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide, which has a significantly different chemical structure and function than tacrolimus.

Moreover, there is no single method for solubilizing all poorly soluble drugs. As a result, numerous techniques have been developed for solubilizing such drugs. The effectiveness of these techniques varies considerably from drug to drug, and a formulator cannot predict which technique will be successful. Accordingly, a skilled formulator would not have known based on Koretke that a mixture of PEG and poloxamer would be highly effective at delivering tacrolimus in a slow release formulation.

For the foregoing reasons, one of ordinary skill would not have had any motivation to incorporate the *fast* release composition of Koretke in the *sustained* release composition of Yamashita, or a reasonable expectation that a combination of PEG and poloxamer could successfully be used to prepare a high bioavailability, slow release tacrolimus tablet, as presently claimed.

Accordingly, Yamashita and Koretke, taken alone or together do not render obvious the present claims. Applicants respectfully request, therefore, that the rejection be withdrawn.

Double Patenting Rejections

Claims 1-44 and 51 stand provisionally rejected for obviousness-type double patenting over (i) claims 59, 66, 72-74, 83-85 and 90 of copending application no. 10/574,125 (the '125 application) and (ii) claims 1, 3-11, 13-29, 31-34, 36, 37, 40-44 and 53-56 of copending application no. 10/569,863 (the '863 application).

Solely in order to expedite allowance of the present application, submitted herewith is a terminal disclaimer over the '125 or '863 pending applications. Accordingly, Applicants respectfully request that these provisional rejections be withdrawn.

Claims 1-44 and 51 stand provisionally rejected for obviousness-type double patenting over claims 1-50 of copending application no. 11/885,992 (the '992 application). The '992 application has been abandoned, rendering this rejection moot.

In view of the above amendments and remarks, Applicants believe the pending application is in condition for allowance. If there are any other issues remaining, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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